REMARKS

Claims

Claims 1–3 and 9–13 are currently under examination with claims 4–8 withdrawn from consideration due to restriction/election. Claims 14 and 15 are added by this paper.

Claim amendments

Support for the amendment of the claims can be found in, for example, the first complete paragraph in page 3, and the paragraphs bridging pages 4 and 5 of the originally-filed specification. New claims 14 and 15 are supported, at least, by the disclosure contained in the last paragraph of page 4 of the originally-filed specification.

The amendment of claim 2 is self-explanatory.

It is respectfully submitted that the claim amendments do not raise new matter. Entry thereof is earnestly solicited.

Rejection under §112, ¶2

Claims 1–3, 9, 10 and 12 are rejected under this section as allegedly being indefinite. Reconsideration is respectfully requested.

The rejection of claims 1, 3 and 9 for allegedly reciting "an incomplete method claim" is moot in view of the forgoing amendments.

Applicants respectfully disagree with the Examiner's contentions of indefiniteness and/or lack of written description of functionally equivalent polypeptides and/or response elements. A review of the specification, for example, page 4, paragraphs 1–3, provides many examples of functionally equivalent Rev-erb polypeptides and/or response elements. As such, the PTO's contentions are without merit. However, in order to facilitate prosecution, the claims have been amended. Applicants' amendment of the claims is not to be construed with acquiescence to this or any other ground of rejection. It is submitted that the rejection is moot in view of the amendments.

The rejection of claims 10 and 12 for allegedly failing to recite "at which point…the expression level of apolipoprotein C-III is to be measured" is moot in view of the amendments. Applicants submit that the skilled worker, in view of the totality of the disclosure contained in the Applicants' specification, can reasonably conclude that measurement of expression levels is a means of evaluating the "transcriptional activity," as recited in the independent claims 3 and 9. However in order to facilitate prosecution, the claims have been amended. Withdrawal of the rejection is respectfully requested.

The generic contention that "the method steps, as recited [in claims 3 and 9], are insufficient to accomplish the goal set in the preamble" is respectfully traversed. The rationale for this rejection is provided in the last sentence of the first complete paragraph at page 6 of the Office Action. The Office Action contends that "it is unclear how an assay the [sic] measures binding would characterize or test a mechanism of action of a test substance." Applicants disagree that the preamble of the claim is directed to testing of a mechanism of action, as alleged by the Office Action. The present claims are directed to *a method of screening for a test substance*. Binding-based assays are not only useful, but are also *ab initio* utilized in such screening assays. Moreover, as is commonly understood in the art, screening of lead compounds (for e.g., agonists and antagonists) is at least initially based on the strength of binding to a given target molecule (for example, via measurement of dissociation constants) and specificity of binding to said target. As such, the alleged requirement that the claimed screening methods explicitly recite "action" of the test substances is without scientific and legal merit. Withdrawal of the rejection is respectfully requested.

Applicants therefore respectfully submit that the claim language is sufficiently definite, especially in the context of Applicants' instant specification and the information available to the skilled worker prior to the filing of the instant application. Withdrawal of the rejection is respectfully requested.

Rejection under §112, ¶1

At the outset the instant claims have been amended to recite human Rev-erb polypeptides. This is not to imply that the original claim scope was problematic under US law. Applicants' claims satisfy the statutory requirements under §112, 1st paragraph as established under *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997)), wherein the Lilly Court held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." In the instant application, the disclosure of representative species, for example, human Rev-erb α polypeptide sequences, which fall within the claimed genus of human Rev-erb polypeptides, provides more than an adequate written description of the claimed molecules.

The contention that Rev-erb receptor, as recited in the claims, "encompasses numerous species that are not further described [other than hRev-erbα]" is respectfully traversed. At the outset, it is submitted that the specification explicitly teaches two additional species of Rev-erb

receptors (for example, Rev-erb β and γ), the structural information of which a skilled worker can readily obtain from the replete information on such proteins. See, the paragraph bridging pages 2 and 3 and the references cited therein. The specification also provides a detailed disclosure of functional equivalents thereof, comprising, for example, the ligand-binding site and response-element binding site of the aforementioned Rev-erb proteins (see, *infra*), including functional chimeras thereof. See, in the paragraphs bridging pages 4 and 5 of the originally-filed specification and in the references cited therein and new claims 14 and 15. The utility of such functional equivalents, for example, in biochemical purification and/or in binding-based or 2-hybrid based assay techniques, is clearly described. As such, the PTO's contentions are without merit.

Claims 1–3 and 9–13 are further rejected under this section for allegedly failing to provide adequate written description of functional equivalents of the Rev-erb receptor protein and functional equivalents of the Rev-erb response element(s). Applicants respectfully disagree with this contention. The specification provides detailed written description of the claimed proteins, including response elements which bind thereto. The specification explicitly teaches that these functional equivalents of Rev-erb response elements comprising polynucleotide sequences that are capable of binding to Rev-erb proteins, are art known. As such, the PTO's contentions are without merit.

With respect to the structural information of Rev-erb protein sequences and the claimed variants thereof, inasmuch as the polypeptide sequences of the Rev-erb receptor proteins (for example, Rev-erb-α, β, and γ) were known in the art, the specification need not provide, and preferably omits, explicit description of the structural features thereof. See, *Capon v. Eshhar*, 418 F.3d at 1357, 76 USPQ2d 1078 (Fed. Cir. 2005). For example, based on the art-known polypeptide sequences of full-length Rev-erb-α, β, and γ proteins, the fusion proteins and the chimeras heretofore claimed could be routinely generated and utilized without undue experimentation. The same is true for the structural information of the response elements claimed herein. Withdrawal of the rejection is respectfully requested.

Applicants bring to the Examiner's attention the scientific article by Forman (Molecular Endocrinology, Vol 8, 1253-1261, 1994), which provides information on the structure and domain construction of Rev-erb receptors, including response elements which bind thereto.

Thus, it is evident that Applicants' specification further in view of the references cited therein, clearly provides the information set forth by the U.S. Patent Office as needed to meet the statutory requirements under §112, ¶1. Withdrawal of the rejection is respectfully requested.

Rejection under §102

Claims 1–3 and 9 are rejected under §102(e) as allegedly anticipated by Trueheart (US patent No.: 6,159,705; correctly cited in the IDS). Applicants respectfully traverse this rejection.

Trueheart discloses a rapid, effective assay for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate the activity of a cellular protein, e.g., a receptor or ion channel. See ABSTRACT of USP'705. Under "Receptors" section, Trueheart teaches that examples of such receptors are cytokine receptors (e.g., IL-2, IL-4, IL-6, IL-7 and IFNγ), multi-subunit immune recognition receptors (e.g., B cell antigen receptors, T cell antigen receptors, Fc receptors or CD22), nuclear receptors (e.g., steroid hormone receptor, vitamin D receptor, ecdysone receptor, retinoic acid receptor and thyroid hormone receptor, estrogen receptor, progesterone receptor, androgen receptor, mineralocorticoid receptor, at least 40 orphan receptors, including. orphan nuclear receptors represented by NGF1, FTZ-F1, Rev-erbs, and RARs), receptor tyrosine kinase receptors (four broad sub-groups comprising, e.g., sub-group I (epidermal growth factor (EGF) receptor-like), sub-group II (insulin receptor-like and the eph/eck family contain cysteine-rich sequences), subgroup III (platelet-derived growth factor (PDGF) receptor-like) and sub-group IV (fibroblast growth factor (FGF) receptors). There is no mention of *human Rev-erb* of the present invention and more specifically, human Rev-erbα as disclosed herein.

With respect to the generic disclosure of nuclear receptors, Trueheart teaches assay techniques which utilize hormone-dependent reporter constructs. It is taught that glucocorticoid response elements (GREs) and thyroid receptor enhancer-like DNA sequences (TREs) can be used to drive expression of reporter construct in response to hormone binding to hormone receptors. The reference proceeds to disclose a number of steroid hormone and thyroid hormone responsive transcriptional control units. Trueheart is absolutely silent with respect to human Rev-erb response elements, as claimed herein.

It is respectfully submitted that Trueheart's disclosure which generically teaches an orphan steroid receptor (Rev-erb) and reporter constructs of other steroid receptors cannot anticipate what is claimed by the instant invention. It is required that for anticipation, the cited reference, either explicitly or inherently, teach all the elements of Applicants' claims. Trueheart is absolutely silent with respect to hRev-erb polypeptides and response elements thereof. See, claims 1, 2, 3 and 9. Moreover, nothing in the reference in any way inevitably leads a skilled worker to combine Rev-erb protein, on which the Office Action relies, with any reporter construct which happens to meet the structural elements of the present claims. Anticipation cannot be achieved where enormous picking and choosing is needed. *In re Arkeley*, 455 F.2d 586 (CCPA 1972).

Claims 10–13 are rejected under §103(a) as allegedly rendered obvious by the aforementioned Trueheart (USP'705) in view of vu-Dac et al (*JBC*, 1998), Fraser (*JBC*, 1997) and Auwerx (*Atherosclerosis*, 1996). This contention is respectfully traversed.

The limitations of the Trueheart reference have been analyzed *supra*. As conceded by the Examiner at page 7 of the Office Action, "The '705 patent does not teach a method comprising measuring the expression level of apolipoprotein C-III (ApoC-III)." The Office Action contends that this aspect of the claimed invention is obtained from vu-Dac and other tertiary references. Applicants respectfully disagree.

With respect to vu-Dac, the Office Action alleges that vu-Dac teaches the effect of Rev-erb α on Apo-I and Apo-111, but concedes that the cited secondary reference is absolutely silent with regard to the effect thereof on Apo C-III expression levels. The Examiner appears to allege that based on Fraser's disclosure that "Apo C-III is closely related to Apo-1 and appears to share regulatory elements," the modulation of transcriptional activity of Apo C-III by Rev-erb would be analogous to the effect thereof on Apo-1. However, this is not the case. vu-Dac and Fraser, even at their broadest interpretation, fail to teach or suggest modulation of Apo C-III expression levels by Rev-erb. More specifically, there is no mention that the interaction of hRev-erb with its cognate response element results in negative regulation of Apo C-III transcriptional activity, as claimed herein. See, amended claim 1 and claim 11.

Trueheart in view of vu-Dac, Fraser and Auwerx also does not render the claims obvious because nothing motivates a skilled worker to choose precisely Rev-erb and combine it with precisely a response element recited in Applicants' claims, especially since the details and examples of the reference would point particularly to other types receptors and response elements. For example, in the preferred embodiments, Trueheart expressly teaches that the methods are applicable for screening of compounds which change the activity of G-protein coupled receptors or EPH receptors. Trueheart discloses more than 60 species of such GPCRs (e.g., α_{1A}-adrenergic receptor, α_{1B}-adrenergic receptor, α_2-adrenergic receptor, α_{2B}-adrenergic receptor, α_1-adrenergic receptor, β-adrenergic receptor, β_3-adrenergic receptor, etc) and more than 30 species of "preferred EPH receptors." See, the SUMMARY OF THE INVENTION section of USP '705. The skilled worker is not motivated to use Rev-erb proteins in combination with any of the Rev-erb response elements taught by the cited secondary reference. Without such motivation, there can be no obviousness. *In re Baird*, 16 F.2d 380 (Fed.Cir. 1994).

Withdrawal of the rejection is respectfully requested.

Applicants bring to the Examiner's attention WO 98/13513, which corresponds to the above-cited USP'705.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

Sagun KC, Reg. No. L0510
Agent for Applicant(s)

/Anthony J. Zelano/

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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